PUBLIC SUMMARY DOCUMENT

Product: Nicotinic Acid, tablets (prolonged release), 500 mg, 750 mg and 1 g, Niaspan®

Sponsor: Alphapharm Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

This submission sought the listing of a prolonged release formulation of nicotinic acid as a restricted benefit for use in combination with an HMG CoA reductase inhibitor (statin) in Type II diabetic patients with dyslipidaemia whose High Density Lipoprotein Cholesterol (HDL-C) levels are inadequately controlled despite monotherapy with a statin.

2. Background

This formulation of nicotinic acid had not previously been considered by the PBAC.

The unrestricted listing for nicotinic acid immediate release tablets 250 mg was deleted from the PBS at the request of the sponsor on 1 December 2005. However, a non-subsidised 250 mg tablet remains available.

3. Registration Status

The TGA registered Niaspan on the 27 February 2006 for "the treatment of mixed dyslipidaemia, and primary hypercholesterolaemia, as adjunctive therapy to diet. Prior to initiating therapy with nicotinic acid, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated."

4. Listing requested and PBAC's View

The submission requested a restricted benefit for use in combination with a HMG CoA reductase inhibitor (statin) in type 2 diabetic patients with dyslipidaemia whose HDL-C levels are inadequately controlled despite monotherapy with a statin. Inadequate control is defined as HDL-C<1 mmol/L after at least 3 month's treatment with a statin.

The PBAC's view was that an authority required restriction would be more appropriate to ensure that the stated objectives of the proposed indication were achieved. The Pre-PBAC response clarified that the sponsor's intention was to seek listing as an add-on treatment in 'at-risk' patients.

5. Clinical place for the proposed therapy

Niaspan will provide add-on treatment for Type 2 diabetic patients with dyslipidaemia whose HDL-C levels are inadequately controlled with a statin alone.

6. Comparator

The submission nominated ezetimibe as the main comparator.

The selection of ezetimibe as the comparator in the submission was not accepted by the PBAC. The PBAC considered nicotinic acid will not replace ezetimibe in clinical practice. It represents a new pharmacological action, not currently available to prescribers under the PBS. The Committee considered the comparator could be placebo, as an add-on to a statin, if the objective of therapy with nicotinic acid is improvement in overall cardiovascular risk, as well as standard-release nicotinic acid (not on PBS).

7. Clinical Trials

The scientific basis of comparison was an indirect comparison of nicotinic acid prolonged release tablets and ezetimibe based on results from:

(i) one randomised trial of prolonged-release nicotinic acid tablets versus placebo over 16 weeks in patients with type 2 diabetes with dyslipidaemia treated with/without a statin (Protocol MA-98-0108, published as Grundy et al, 2002); and

(ii) one randomised trial comparing the addition of ezetimibe to statin therapy with a doubling of the statin dose over 24 weeks in patients in patients with type 2 diabetes and dyslipidaemia treated with a statin (Gaudiani et al 2005).

The trial published at the time of the submission were as follows:

Trial/First author	Publication title	Citations
Protocol MA-98-0108/Grundy SM	Efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidaemia associated with type 2 diabetes	Arch Intern Med. 2002; 162:1568-76.
Gaudiani et al.	Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients	Diabetes Obes Metab 2005; 7: 88-97.

8. Results of Trials

According to the analyses comparing nicotinic acid + statin (ie, the subgroup of patients in Protocol MA-98-0108) and ezetimibe 10 mg + simvastatin 20 mg (ie, patients in Gaudiani et al, 2005 trial), there appeared to be:

(i) numerically larger increase in HDL-C from baseline and numerically larger decrease in triglyceride from baseline favouring nicotinic acid over ezetimibe;

(ii) numerically larger decrease in LDL-C and total cholesterol from baseline favouring ezetimibe over nicotinic acid;

(iii) numerically larger decrease in TC: HDL-C ratio from baseline favouring nicotinic acid over ezetimibe; and

(iv) no effect on LDL-C due to nicotinic acid.

The PES Commentary advised, the drawing of conclusions based on the above data was problematic due to the lack of a common reference across the trials and due to potential differences in the baseline characteristics of patients recruited to each trial.

A matter of concern was the worsening of glycaemic control associated with the high dose nicotinic acid. According to the analyses, greater increases from baseline were generally observed for both HbA_{1c} and fasting blood glucose in the nicotinic acid + statin subgroup in Protocol MA-98-0108 compared to the ezetimibe + simvastatin group in Gaudiani et al (2005), though generally not statistically significant.

In Protocol MA-980108, the proportion of patients experiencing flushing were reported as 5/45 (11.1%) for placebo, 30/45 (66.7%) for nicotinic acid 1,000mg and 35/52 (67.3%) for nicotinic acid 1,500mg. The maximum intensity of flushing events was generally mild to moderate in severity. No cases of myopathy were reported in Protocol MA-98-0108 and Gaudiani et al (2005). There were no other important differences in safety parameters across the two trials.

9. Clinical Claim

The implicit claim in the submission was that nicotinic acid had advantages in terms of effectiveness over ezetimibe and was associated with a similar safety profile.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was valid only if the PBAC accepted the submission's implicit claim that nicotinic acid had advantages in terms of effectiveness (in terms of effect on TC: HDL-C ratio) over ezetimibe. The resources included were drug costs.

The trial-based incremental cost per extra point reduction in TC: HDL-C ratio was dominated by nicotinic acid which was claimed to be less expensive and more effective than ezetimibe.

A modelled economic evaluation against placebo was presented. The base case modelled incremental discounted cost per extra QALY gained was either < $15,000 or in the range $15,000 - $45,000 over 52, or 44 years, for nicotinic acid 1,000 mg/day vs placebo, depending on the model used (model based on risk equations from UK Prospective Diabetes Study (UKPDS) or from Framingham Heart Study (FHS), respectively); < $ 15,000 over 52, or 44 years, for nicotinic acid 1,500 mg/day vs placebo, depending on the model used (model based on risk equations from UKPDS or from FHS, respectively)

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was > 200,000 in 2010, while the financial cost per year to the PBS (excluding co-payments) was < $10 million in 2010.

12. Recommendation and Reasons

The PBAC considered an authority required restriction would be more appropriate to ensure that the stated objectives of the proposed indication are achieved.

The selection of ezetimibe as the comparator in the submission was not accepted by the PBAC. The PBAC considered nicotinic acid will not replace ezetimibe in clinical practice. It represents a new pharmacological action, not currently available to prescribers under the PBS. The Committee considered the comparator could be placebo, as an add-on to a statin, if the objective of therapy with nicotinic acid is improvement in overall cardiovascular risk, as well as standard-release nicotinic acid (not on PBS).

The Pre-PBAC response clarified that the intent was to seek listing as an add-on treatment in 'at-risk'patients.

More importantly, the PBAC did not consider the submission's implicit claim that nicotinic acid prolonged release tablets are more effective (in terms of effect on TC: HDL-C ratio) and no worse in terms of safety than ezetimibe, was reasonable. Nicotinic acid when used as in the trials presented , had no effect on LDL-C and only a small effect on triglycerides but only at the higher dose. In addition, there is no clinical trial evidence demonstrating that raising HDL-C improves clinical outcomes. Therefore, the validity of raising HDL-C as a surrogate outcome has not been established. All other lipid-lowering drugs already listed on the PBS had either clinical outcomes data and/or evidence of lowering LDL-C, hence TC:HDL ratio. The primary mechanism by which nicotinic acid lowers the TC:HDL ratio is via HDL-C rather than LDL-C. The impact of this different mechanism on cardiovascular events is unknown. This is also a fundamental concern with Framingham based modelled economic evaluation which has the TC:HDL ratio as a driver.

The PBAC noted the Pre-PBAC Response advice that overall it has been concluded from prospective population studies that for every 0.025 mmol/L increase in HDL-C, cardiovascular risk is reduced by 2 to 5%. However, the Committee considered that this clinical benefit seen in epidemiological data could not be assumed to flow from raising HDL-C with a drug.

The PBAC noted the trial evidence presented showed no effect was seen on LDL with nicotinic acid in this setting (ie with background statin therapy), whereas it had a significant TC-lowering effect (10%), in the *Coronary drug project: experience with niacin* (Coronary Drug Project Research Group. Berge KG, Canner PL. Eur J Clin Pharm 40 Supp 1: S49-51; 1991).

There was concern that the high doses of nicotinic acid worsen both HbA1c and fasting blood sugar levels. The Pre-PBAC response, while noting that similar outcomes were observed in the Gaudiani trial for the ezetimibe and simvastatin arm, and the simvastatin 40 mg arm respectively, pointed out that in terms of HBA1c there was a statistically significant difference only in the 1500 mg nicotinic acid arm (p=0.047) in the ITT analysis (MA 98-0108).

Given the PBAC's views in relation to the comparator and the implicit clinical claim, the economic evaluation was not pivotal to its recommendation. The preliminary economic evaluation was not relevant. However, the PBAC considered the placebo based models would have been acceptable if based on appropriate clinical data. Specific comments with respect to the two models presented included:

- The second model was based on the UKPDS risk equation which overestimates the baseline risk in the Australian population.

- The acceptability of the assumption in the model of differences in baseline parameters for patients in the two arms of the model based on non-significant differences in the trial. It was unclear whether the model-derived differences in effectiveness and cost-effectiveness are driven by differences in baseline characteristics or by true treatment differences.
- The use in the UKPDS model of EQ5D utility decrements may overestimate the true quality of life decrements because of the assumption of an additive effect of multiple complications and because a feature of the EQ5D instrument is that because it has relatively few dimensions and levels to describe health states, when a difference is detected, the numerical value can appear disproportionately large.

The PBAC therefore rejected the submission on the basis the comparator was not appropriate and lack of clinical evidence to support the implicit claim that an increase in HDL levels reduces cardiovascular risk.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Alphapharm looks forward to working with the PBAC to address the issues raised by the Committee**.**